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Graphical Abstract

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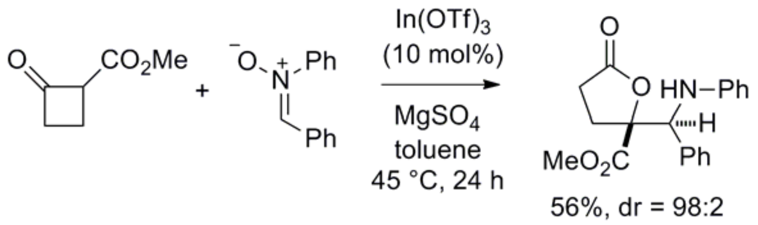

Indium(III) triflate-catalyzed reaction of 2-carbomethoxycyclobutanone with nitrones

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ABSTRACT

2-Carbomethoxycyclobutanone reacted with N-phenyl-C-arylnitrones to afford methyl 5-oxo-2-[aryl(phenylamino)methyl]tetrahydrofuran-2-carboxylates by the catalysis of indium(III) triflate in the presence of magnesium sulfate.

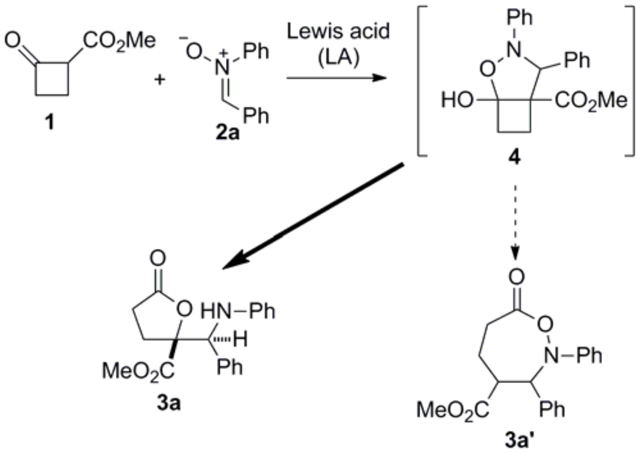
Keywords

Nitrone ; γ-Lactone ; Indium(III) triflate ; Cyclobutanone ; Rearrangement

Nitrones are useful synthetic intermediates in organic synthesis and have been used mainly in the 1,3-dipolar cycloaddition with olefins to give isoxazolidines.[1] In addition to olefins, nitrones reacted with donor-acceptor cyclopropanes and cyclobutanes for [3+3][2,3] and [4+3][4] cycloadditions, respectively. Moreover, nucleophilic additions to nitrones have been studied for carbon nucleophiles such as Grignard reagents,[5] cyanide ion,[6] and sodium salts of diethyl malonate.[7] We were interested in a reaction of 2-carbomethoxycyclobutanone (**1**)[8] with nitrones because four-membered ketoester **1** can work as a carbon nucleophile and it has a characteristic feature of facile ring cleavage.[9] Thus, we tried to synthesize a seven-membered ring compound **3a'** by nucleophilic addition of **1** to nitrone **2a** followed by ring cleavage of four-membered ring of **4** (Scheme 1). However, we found unexpected formation of a γ-butyrolactone derivative **3a** by Lewis acid-catalyzed reaction of nitrone **2a** with **1**, and we report here the results.

Scheme 1

Formation of γ-buryrolactone **3a** by Lewis acid-catalyzed reaction between **1** and **2a**



First, various Lewis acids were screened in a model reaction between **1** and nitrone **2a** to afford γ-butyrolactone **3a** (Table 1). In the absence of a Lewis acid, cyclobutanone **1** was not react with **2a** at refluxing temperature of toluene, and even ring cleavage of **1** did not observed by TLC analysis (Entry 1). The use of catalytic amounts (10 mol%) of the typical Lewis acids $TiCl_4$, BF_3-EtO_2 and Me_3SiOTf gave the desired product **3a** in 16%, 34% and 27% yields, respectively (Entries 2–4), while the use of more than stoichiometric amounts (1.3 equiv) of these Lewis acids did not afford **3a** at all. Catalytic amounts (10 mol%) of several metal triflates were then tested in this reaction, and it was found that $In(OTf)_3$ promoted the reaction most efficiently (Entries 5–11). The Brönsted acid TsOH also catalyzed the reaction, but the reaction proceeded sluggishly (Entry 12). It should be noted that high diastereoselectivity was observed in the Lewis acid-catalyzed reaction of **1** and **2a** as shown in Table 1. We employed $In(OTf)_3$ in the following experiments since the reaction time was shorter than that for BF_3-OEt_2 (Entries 3 and 11).[10]

Table 1

Effects of Lewis acids in a reaction of **1** and **2a** to give γ-butyrolactone **3a** (eq 1)[a]

Entry	Lewis acid	Time (h)	Isolated yield (%)	dr[b]
1[c]	none	48	0	
2	$TiCl_4$	48	16	99:1
3	BF_3-Et_2O	48	34	96:4
4	Me_3SiOTf	18	27	98:2
5	AgOTf	24	29	96:4
6	$Zn(OTf)_2$	23	18	97:3
7	$Cu(OTf)_2$	53	1	98:2
8	$Yb(OTf)_3$	19	12	96:4
9	$La(OTf)_3$	29	17	98:2
10	$Sc(OTf)_3$	19	19	96:4
11	$In(OTf)_3$	20	32	96:4
12	TsOH-H_2O	48	20	96:4

[a] Unless otherwise mentioned, the following reaction conditions were used: cyclobutanone **1** (1.0 equiv), nitrone **2a** (1.3 equiv), and Lewid acid (10 mol%) were reacted in toluene at 45 °C.

[b] Determined by ^1H NMR.

[c] Reaction conditions: 45 °C (24 h) and reflux (24 h).

Next, effects of additives in the $In(OTf)_3$-catalyzed reaction of **1** and **2a** were investigated (Table 2). Some drying agents were employed as additives because benzaldehyde was detected by TLC analysis in the above-mentioned Lewis acid screening. The use of molecular sieves 4A and 5A was not effective and led to

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considerably lower yields of the desired product **3a** (Entries 2 and 3). The addition of Na_2SO_4 did not cause any change compared with the case of no additives, whereas the use of $MgSO_4$ greatly improved the yield of **3a** to 56% (Entries 4 and 5). TLC analysis of the reaction mixture showed smooth consumption of cyclobutane **1** in the presence of $MgSO_4$, but benzaldehyde was still detected even in the presence of $MgSO_4$. $MgSO_4$ did not work as a Lewis acid in this reaction because the product **3a** was detected only in a trace amount by using $MgSO_4$ in the absence of $In(OTf)_3$ (Entry 6). Therefore, at present, the role of $MgSO_4$ is not clear. The use of $Mg(ClO_4)_2$ gave the desired product **3a** in 6% yield (Entry 7), and it was found that $MgSO_4$ was an appropriate additive in the present $In(OTf)_3$-catalyzed reaction.[11]

Table 2

Effects of additives in an $In(OTf)_3$-catalyzed reaction of **1** and **2a** to afford **3a** (eq 1)[a]

Entry	Additive	Time (h)	Isolated yield (%)	dr[b]
1	none	24	36	96:4
2	MS4A	48	0	
3	MS5A	72	5	99:1
4	Na_2SO_4	14	39	97:3
5	$MgSO_4$	24	56	98:2
6[c]	$MgSO_4$	48	trace	
7	$Mg(ClO_4)_2$	24	6	87:13

[a] Reaction conditions: cyclobutanone **1** (1.0 equiv), nitrone **2a** (2.0 equiv), $In(OTf)_3$ (10 mol%), and additive (300 mg/mmol of **2**) were reacted in toluene at 45 °C.

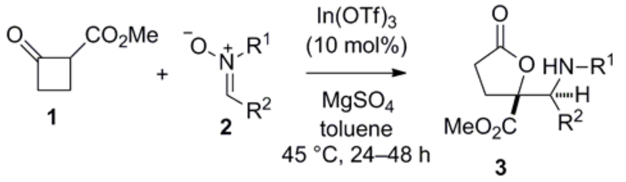
[b] Determined by ^1H NMR.

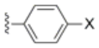
[c] In the absence of $In(OTf)_3$.

The scope and limitations of the reaction of cyclobutanone **1** and nitrones were investigated by employing various nitrones **2b–g** (Table 3). *N*-Phenyl-*C*-arylnitrones **2b–d** with electron-withdrawing groups such as fluoro, chloro, and bromo groups at the *p*-position of the phenyl ring gave results comparable to those with the parent unsubstituted nitrone **2a** (Entries 1–3). Substitution with a methyl group resulted in a slightly decreased yield of **3e** (Entry 4). The use of a nitrone **2f** bearing a *C*-2-naphthyl group instead of the *C*-phenyl group lowered the yield of the corresponding γ-butyrolactone **3f** (entry 5). *C*-Alkyl nitrone **2g**, which was prepared in situ from 3-phenylpropanal and *N*-phenylhydoxylamine, reacted with **1** to afford **3g** in 24% yield (Entry 6) whereas *N*-methyl nitrone **2h** did not react with **1** (Entry 7). Stereochemistry of **3** was determined by X-ray crystallography of **3d**.

Table 3

Scope and limitations of $In(OTf)_3$-catalyzed reaction of cyclobutanone **1** and nitrone **2b–g** to give γ-butyrolactone **3b–g**[a]



Entry	2	R^1	R^2		3	Yield (%)	dr[b]
1	**2b**	Ph		X = F	**3b**	51	96:4
2	**2c**	Ph		X = Cl	**3c**	46	97:3
3	**2d**	Ph		X = Br	**3d**	51	97:3
4	**2e**	Ph		X = Me	**3e**	41	98:2
5	**2f**	Ph	2-Naphthyl		**3f**	40	95:5
6	**2g**	Ph	$(CH_2)_2Ph$		**3g**	24	93:7
7	**2h**	Me	Ph		**3h**	0	

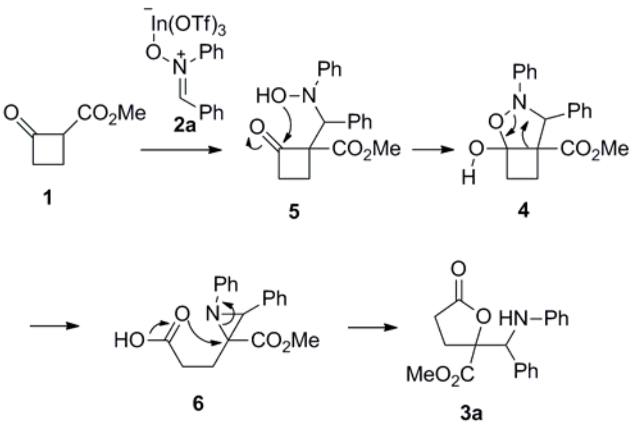
[a] Reaction conditions: cyclobutanone **1** (1.0 equiv), nitrone **2** (2.0 equiv), $In(OTf)_3$ (10 mol%), and $MgSO_4$ (300 mg/mmol of **2**) were reacted in toluene at 45 °C.

[b] Determined by ^1H NMR.

A proposed mechanism for the $In(OTf)_3$-catalyzed reaction between cyclobutanone **1** and nitrone **2a** is shown in Scheme 2. Nucleophilic attack of cyclobutanone **1** to nitrone **2a** which is activated with $In(OTf)_3$ gives hydroxylamine **5**, in which intramolecular attack of the hydroxyl group to the carbonyl group of cyclobutanone gives isoxazolidine derivative **4**.[12] Valence rearrangement[13] of the isoxazolidine ring of **4** gives aziridin-2-yl carboxylic acid **6**. Intramolecular attack of the carboxylic acid group to the aziridine ring gives γ-butyrolactone **3a**. Each step shown in Scheme 1 can be catalyzed with $In(OTf)_3$.

Scheme 2

A proposed mechanism for $In(OTf)_3$-catalyzed reaction of **1** and nitrone **2a** to γ-butyrolactone **3a**



In conclusion, we found a new method for synthesis of functionalized γ-butyrolactone by a reaction of 2-carbomethoxycyclobutanone[14] with *N*-phenyl-*C*-arylnitrones. This reaction was effectively promoted by using a catalytic amount of $In(OTf)_3$ in the presence of $MgSO_4$. Valence rearrangement of an isoxazolidine intermediate followed by intramolecular attack of a carboxylate group to an aziridine ring was proposed for the formation of γ-butyrolactone.

Acknowledgments

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10. Use of other solvents such as dichloromethane, THF, and acetonitrile gave **3a** in low yields.
11. Under the reaction conditions of entry 5 (Table 1), the starting material **1** was completely consumed, and some very polar co-products were detected by TLC analysis.
12. A concerted mechanism for [3+2] cycloaddition between an enol form of **1** and nitrone **2a** is also possible for generation of **4**. [3+2] Cycloaddition of nitrones and silyl enol ethers: (a) Hosomi, A.; Shoji, H.; Sakurai, H. *Chem. Lett.* **1985**, 1049; (b) Dhavale, D. D.; Trombini, C. *J. Chem. Soc., Chem. Commun.* **1992**, 1268; (c) Camiletti, C.; Dhavale, D. D.; Gentilucci, L.; Trombini, C. *J. Chem. Soc. Perkin Trans. 1* **1993**, 3157.
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14. Indium(III) triflate-catalyzed reaction of nitrone **2a** with ethyl 2-oxocyclopentanecarboxylate or ethyl 2-oxocyclohexanecarboxylate did not afford the corresponding lactones

Supplementary Material

Supplementary data associated with this article can be found in the online version.